

COMBAT & OPERATIONAL STRESS

Research Quarterly

A Word from the Editor:

Dear Colleagues,

We are pleased to introduce this compilation of highly relevant research on combat and operational stress, including recent findings on the etiology, course, and treatment of Post-traumatic Stress Disorder (PTSD). The intent of this quarterly publication is to facilitate translational research by providing busy clinicians with up-to-date findings with potential to guide and inform evidenced-based treatment. We encourage you to not only use the knowledge gained here to apply to your practice, but also share the information with colleagues to initiate discussions about best practices.

In this first quarterly edition we have highlighted relevant peer-reviewed research from the preceding three months. If you have an article or other piece you would like to include in subsequent publications, please contact the editor at kimberly.schmitz@med.navy.mil. If you are interested in further pursuing a research study involving combat and operational stress, but need assistance, please contact the NCCOSC Research Facilitation Assistant Department Head, Dr. Jennifer Webb-Murphy, at 619-532-8889 or jennifer.murphy@med.navy.mil.

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BRAIN AND COGNITION

Anterior cingulate activity to salient stimuli is modulated by autonomic arousal in posttraumatic stress disorder

Sample: Individuals with PTSD and healthy controls
N= 22

Variables: Anterior cingulate activity, skin conductance responses, arousal, PTSD

Key findings: PTSD participants had less ventral anterior cingulate (vACC) activity than controls in the presence of skin conductance responses (SCR) but not when SCR was not present, suggesting that vACC reduction in PTSD occurs only when arousal networks are engaged.

Summary and implications: Disturbed regulation of arousal has been implicated in PTSD pathology. Neuroimaging studies have reported both increased and decreased anterior cingulate activity (ACC) in PTSD, although the studies varied in whether participants' arousal networks were engaged (such as through threatening stimuli). The aim of this study was to test if reductions in ventral ACC activity in PTSD are specific to stimuli that engage arousal networks. The authors compared PTSD participants to non-traumatized controls while performing

a cognitive task that required responding to salient, non-trauma-related auditory target tones embedded in lower frequency background tones. During these tasks, functional magnetic imaging (fMRI) and skin conductance responses (SCR) were recorded to determine when arousal networks were engaged. In averaged target-background analyses, the PTSD participant group showed greater dorsal ACC activity, supramarginal gyrus activity, and hippocampal activity. However, PTSD participants had reduced vACC activity to target tones when SCR responses were present, suggesting arousal. The reduction in vACC did not occur without arousal in without-SCR responses. This suggests that this reduction in vACC in PTSD participants occurs only when arousal networks are engaged. Reduced vACC activity to threat is thought to reflect impairment in regulating arousal networks in PTSD. Further neuroimaging studies should account for variations in arousal, as this may affect their conclusions.

Felmingham, K.L., Williams, L.M., Kemp, A.H., Rennie, C., Gordon, E. & Bryant, R.A. (2009). Anterior cingulate activity to salient stimuli is modulated by autonomic arousal in posttraumatic stress disorder. *Psychiatry Research*, 173 (1), 59-62.

The organization of autobiographical and nonautobiographical memory in posttraumatic stress disorder (PTSD)

Sample: Trauma survivors with and without PTSD, nontraumatized healthy adult controls

N= 111

Variables: PTSD, nonautobiographical memory, autobiographical memory

Key findings: Trauma memories were more disorganized than memories of an unpleasant event in the PTSD group in comparison with the non-PTSD group, but no differences were found for memory organization of nonautobiographical material among trauma survivors with and without PTSD and nontraumatized controls.

Summary and implications: Disorganized trauma memory appears to be an important part of the pathogenesis of PTSD, but whether nonautobiographical memory is also impaired in PTSD has not been determined. This study examined impairment of autobiographical versus nonautobiographical memory in PTSD and investigated whether memory disorganization of the traumatic event exceeds the level of general verbal memory impairment in a traumatized person. This study had three groups: trauma survivors with PTSD (n=26), individuals exposed to trauma without PTSD (n=55), and healthy, nontraumatized adults (n=30). Each participant was given the Narrative Memory Test, which measures nonautobiographical content memory and sequence memory performance in free recall and recognition. Traumatized participants also gave a detailed description of the traumatic event and an unpleasant event to measure autobiographical memory. The results showed that trauma memories were more disorganized than memories of an unpleasant control event in participants with PTSD versus traumatized participants without PTSD. Participants with PTSD, compared to traumatized participants without PTSD and nontraumatized controls, did not show significantly worse performance in nonautobiographical content memory. The findings of this study support impairment in organization of autobiographical traumatic event memory but not of nonautobiographical memory in PTSD.

Jelinek, L., Randjbar, S., Seifert, D., Kellner, M. & Moritz, S. (2009). The organization of autobiographical and nonautobiographical memory in posttraumatic stress disorder (PTSD). *Journal of Abnormal Psychology*, 118 (2), 288-98.

Dysfunctions of cortical excitability in drug-naïve posttraumatic stress disorder patients

Sample: Drug-naïve PTSD patients and healthy controls

N= 36

Variables: γ -amino-butyric acid (GABA), glutamate, PTSD

Key findings: Participants with PTSD showed impairment of GABA_A-ergic paired-pulse short-latency intracortical inhibition (SICI), which was reversed toward facilitation in both hemispheres in half of the patients, marked increase of glutamatergic intracortical facilitation (ICF) in the right hemisphere, and right-sided impairment of paired-pulse short-latency afferent inhibition (SAI).

Summary and implications: The aim of this study was to use transcranial magnetic stimulation (TMS) to find a pattern of cortical excitability changes in PTSD, reflecting GABA and glutamate balance and dysfunction. The authors also sought to determine whether some of the TMS-related variables are related to clinical features. Twenty PTSD patients without comorbidity who had never taken psychotropic medications and sixteen matched healthy controls were tested bilaterally with TMS. The PTSD patients showed bilateral SICI impairment, right-sided SAI impairment and increased right-sided ICF. Right-lateralized dysfunctions of cortical excitability correlated with illness duration and avoidance symptoms. A bilateral decrease of GABA_A-ergic function is probably the result of the pattern of cortical excitability accompanying PTSD symptoms. However, because of the complexity of each TMS variable and the lack of reliable glutamate tracers, this theory has not yet been strongly supported by data. More research into this area may help discover novel pathophysiological abnormalities of PTSD, possibly leading to new treatments.

Rossi, S., De Capua, A., Tavanti, M., Calossi, S., Polizzotto, N.R., Mantovani, A., et al. (2009). Dysfunctions of cortical excitability in drug-naïve posttraumatic stress disorder patients. *Biological Psychiatry*, 66 (1), 54-61.

PSYCHO-BIO

Brain-derived neurotrophic factor plasma levels in patients suffering from post-traumatic stress disorder

Sample: Male and female PTSD outpatients and healthy controls

N= 36

Variables: PTSD, brain-derived neurotrophic factor plasma levels

Key Findings: Brain-derived neurotrophic factor plasma levels were significantly lower in patients with PTSD compared to healthy controls and may play a role in how the disorder affects normal biological functioning.

Summary and Implications: Stress has been linked to decreased expression of brain-derived neurotrophic factor (BDNF), which promotes neuron proliferation, in a number of human and animal studies. Although lower BDNF plasma levels have been associated with traumatic events in patients with affective disorders, it is largely unknown whether PTSD has a similar effect on BDNF levels. BDNF levels were analyzed in 18 drug-free (no current or lifetime psychotropic medication) outpatients with a diagnosis of PTSD and 18 drug-free healthy control subjects. Results of this investigation concluded that BDNF levels were significantly lower in PTSD patients than in the control subjects ($p < .001$), but no significant differences were found in BDNF levels based upon number of lifetime traumas or time since clinical assessment. The findings suggest that BDNF may play a role in the pathophysiology of PTSD.

Dell'osso, L., Carmassi, C., Del Debbio, A., Dell'osso, M.C., Bianchi, C., da Pozzo, E., et al. (2009). Brain-derived neurotrophic factor plasma levels in patients suffering from post-traumatic stress disorder. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, 33 (5), 899-902.

Levels of the potential biomarker p11 in peripheral blood cells distinguish patients with PTSD from those with other major psychiatric disorders

Sample: Patients with either PTSD, major depressive disorder (MDD), bipolar disorder (BP), schizophrenia (SCZ) or no psychiatric condition (controls)

N= 79

Variables: p11 mRNA, cortisol, PTSD, MDD, BP, SCZ

Key findings: PTSD patients had p11 mRNA levels significantly lower than controls, while patients with MDD, BP and SCZ all had p11 levels significantly higher than controls. Levels of cortisol in PTSD patients did not differ from controls.

Summary and implications: PTSD patients often have other comorbid psychiatric conditions, and it can be difficult to distinguish the conditions and correctly diagnose these patients. Some preliminary evidence has pointed to changes in expression of p11 mRNA in the brain tissue of PTSD patients; thus, this mRNA could be an important biomarker to aid in the diagnosis of PTSD and possibly other psychiatric conditions. Glucocorticoid hormones may play a role in the expression changes in p11 mRNA in PTSD patients. The authors investigated p11 mRNA levels in the peripheral blood mononuclear cells (PBMC) of patients with PTSD (n=13), MDD (n=16), BP (n=24), SCZ (n=12) and healthy controls (n=14). To determine the role of glucocorticoids, the authors also investigated levels of cortisol and glucocorticoid receptor (GR) mRNA in PTSD patients and controls. Patients with PTSD had significantly lower levels of p11 mRNA in PBMCs than controls, while patients with MDD, BP and SCZ had significantly higher levels. Levels of cortisol in PTSD patients were not different from controls, but GR mRNA levels in PBMCs were significantly lower than controls, although GR expression levels did not correlate with p11 expression levels in PTSD patients. Of note, the findings of p11 down-regulation in PBMCs of PTSD patients differ from previous studies that have found up-regulation of p11 in brain tissue of PTSD patients; this could reflect tissue-specific changes or variations in trauma or disease stage of the patient populations utilized. This study provides preliminary evidence that p11 mRNA levels in PBMCs could potentially serve as a biomarker for differentiating PTSD from other psychiatric disorders, although further study is needed to confirm these findings.

Su, T.P., Zhang, L., Chung, M.Y., Chen, Y.S., Bi, Y.M., Chou, Y.H., et al. (in press). Levels of the potential biomarker p11 in peripheral blood cells distinguish patients with PTSD from those with other major psychiatric disorders. *Journal of Psychiatric Research*.

Biomarkers of blast-induced neurotrauma: profiling molecular and cellular mechanisms of blast brain injury

Sample: Brain-injured individuals and animals

Variables: Biomarkers, traumatic brain injury (TBI), molecular pathways

Key findings: A set of biomarkers has been discovered that together can detect TBI and predict its outcome. These include

the proteins S-100 β , neuron specific enolase (NSE), glial fibrillary acidic protein (GFAP), and myelin basic protein (MBP).

Summary and implications: This article reviewed biomarkers that have been found for the detection of TBI. The authors investigated past research on the proteins S-100 β , neuron specific enolase (NSE), glial fibrillary acid protein (GFAP), and myelin basic protein (MBP). These proteins are not specific enough to be used individually, but when they are used in conjunction with each other they can detect TBI and predict its outcome. The authors also reviewed several techniques for inducing brain injury in animals to simulate TBI in the laboratory environment, such as controlled blast exposure; each has its own distinct pathophysiological characteristics and can be exploited to discover new diagnostic biomarkers. This review draws some important conclusions from past research about which biomarkers and molecular pathways are involved in various forms of TBI and can predict the outcome of a specific TBI injury.

Svetlov, S.I., Lerner, S.F., Kirk, D.R., Atkinson, J., Hayes, R.L. & Wang, K.K. (2009). Biomarkers of blast-induced neurotrauma: profiling molecular and cellular mechanisms of blast brain injury. *Journal of Neurotrauma*, 26 (6), 913-21.

Cortisol metabolic predictors of response to psychotherapy for symptoms of PTSD in survivors of the World Trade Center attacks on September 11, 2001

Sample: Survivors of the September 11, 2001, World Trade Center attacks seeking treatment for PTSD symptoms

N= 28

Variables: Cortisol and its metabolites, PTSD symptoms, treatment response

Key findings: 5 α -reductase activity was significantly lower in participants who did not respond to psychotherapy for PTSD compared to participants who did respond to therapy at the pre-treatment time point (prior to therapy), and may be a predictor of PTSD psychotherapy treatment non-response.

Summary and implications: Lower cortisol levels may be a risk factor for PTSD, but cortisol levels may be altered as a consequence of developing PTSD or receiving PTSD treatment. The aim of this study was to examine levels of cortisol and its metabolites in individuals with PTSD symptoms to investigate the association with PTSD and if such biological alterations are observed in these individuals. The study enrolled 28 survivors of the September 11, 2001 terror attacks on the World Trade Center who sought treatment for PTSD symptoms. Participants received four sessions of either exposure therapy or supportive counseling, then 10 sessions of prolonged exposure in a specialized PTSD treatment program. Cortisol and levels of its metabolites were measured pre-treatment, at treatment completion, and three months post-treatment. The results show that activity of 5 α -reductase, which metabolizes cortisol, was significantly lower in participants who did not respond to psychotherapy for PTSD at pre-treatment compared to participants who did respond to therapy. Indices of 5 α -reductase activity were also significantly lower among non-responders compared to responders in repeated measures analyses across the three time points. Cortisol levels also declined over time in the non-responder group so that they

were significantly lower than levels in responders at follow-up. Avoidance symptom severity was negatively correlated with indices of 5 α -reductase activity at pre-treatment. Total PTSD severity scores and symptom cluster severity were also negatively correlated with indices of 5 α -reductase activity at follow-up. These results are consistent with past observations that low cortisol levels correlate with high PTSD symptom severity. The results from this study also suggest that cortisol levels may continue to decline as PTSD becomes chronic or treatment-resistant. Additionally, 5 α -reductase activity may predict non-responsiveness to PTSD psychotherapy. This study's findings have important implications for understanding and effectively treating PTSD in the future.

Yehuda, R., Bierer, L.M., Sarapas, C., Makotkine, I., Andrew, R. & Seckl, J.R. (in press). Cortisol metabolic predictors of response to psychotherapy for symptoms of PTSD in survivors of the World Trade Center attacks on September 11, 2001. *Psychoneuroendocrinology*.

GENETICS

Gene Expression Patterns Associated with Posttraumatic Stress Disorder Following Exposure to the World Trade Center Attacks

Sample: Caucasians with high-magnitude exposure to the World Trade Center attacks, with and without PTSD

N= 35

Variables: Genome-wide expression profiles, PTSD

Key findings: Sixteen genes were identified that were differentially expressed in PTSD patients compared to controls, most of which are involved in hypothalamic-pituitary-adrenal (HPA) axis regulation, signal transduction, or brain and immune cell function. Expression of FKBP5, a regulator of the glucocorticoid receptor (GR), was reduced in PTSD compared to controls.

Summary and implications: Previous literature has identified a role for genetics in the risk of developing PTSD, but specific susceptibility genes have not been confirmed. PTSD has been shown to be associated with enhanced responsiveness of the glucocorticoid receptor (GR), so genes involved in GR regulation could affect PTSD risk. This study compared genome-wide gene expression profiles in subjects with PTSD (n=15) to subjects without PTSD (n=20) who had all been exposed to the World Trade Center attacks. Seventeen probe sets, corresponding to 16 genes, were differentially expressed between those with and without PTSD. Several of these genes are involved in GR regulation, signal transduction, or brain and immune cell function. One of the identified genes, FKBP5, encodes a protein inhibitor of GR. FKBP5 expression was significantly lower in PTSD compared to controls. Another identified gene, STAT5B, is an inhibitor of GR translocation and was also down-regulated in PTSD subjects. These findings are consistent with previous observations of higher GR activity and HPA axis dysfunction in PTSD.

Yehuda, R., Cai, G., Golier, J.A., Sarapas, C., Galea, S., Ising, M., et al. (in press). Gene Expression Patterns Associated with Posttraumatic Stress Disorder Following Exposure to the World Trade Center Attacks. *Biological Psychiatry*.

Looking on the bright side: biased attention and the human serotonin transporter gene

Sample: Individuals without psychiatric diagnoses or psychiatric medications

N= 111

Variables: Cognitive bias, serotonin transporter gene promoter alleles

Key findings: Participants homozygous for the long allele variation in the promoter region of the serotonin transporter gene (5-HTTLPR) showed a significant bias for selectively processing positive affective material and selectively avoiding negative affective material.

Summary and implications: Individuals with depression and anxiety tend to have a bias to pay more attention to negative events than positive or neutral events. The propensity to avoid negative material and selectively process positive emotional information likely plays a role in determining mental health and well-being. This study's aim was to investigate whether the allelic variation in the promoter region of the serotonin transporter gene (5-HTTLPR) is associated with the tendency to selectively attend to positive or negative affective material. Individuals homozygous for the long allele (LL) showed a significant bias for selectively processing positive affective material and selectively avoiding negative affective material. However, this tendency was not seen in participants with the short allele (S or SL). From these findings the authors conclude that allelic variation on a common genetic polymorphism that modulates the synaptic availability of serotonin is associated with the tendency to selectively process either positive or negative information. These findings are noteworthy because they are the first to show this trend in a healthy population, which exposes a known factor for determining both resilience and vulnerability to psychological disorders.

Fox, E., Ridgewell, A. & Ashwin, C. (2009). Looking on the bright side: biased attention and the human serotonin transporter gene. *Proceedings. Biological Sciences / The Royal Society*, 276 (1663), 1747-51.

Serotonin Transporter Gene (SLC6A4) Promoter Polymorphisms and the Susceptibility to Posttraumatic Stress Disorder in the General Population

Sample: Caucasian adult population sample

N= 3,045

Variables: Polymorphisms within the serotonin transporter-linked polymorphic region (5-HTTLPR), lifetime PTSD, number of traumatic events

Key findings: The L_A polymorphism of 5-HTTLPR has an additive relationship with PTSD, and an interaction between the L_A allele and number of traumas was found in participants with

exposure to three or more traumatic events, leading to an even higher risk of PTSD.

Summary and implications: Some recent studies have suggested that polymorphisms in the promoter region of the serotonin transporter gene may be associated with PTSD. The aim of this study was to investigate if polymorphisms in the 5-HTTLPR genotype affect rates of PTSD, and to investigate if these rates are affected by gene-environment interactions between the 5-HTTLPR polymorphisms and number of traumatic events. The participants in this study were assessed using the Structured Clinical Interview for DSM-IV (SCID). Participants were genotyped for three specific alleles of 5-HTTLPR: the short allele (S), and two versions of the long allele that differ by a single nucleotide polymorphism (L_A and L_G). The results show that of the 3,045 participants, 1,663 had been exposed to at least one trauma, and 67 (four percent) met criteria for a lifetime PTSD diagnosis. A dose-response relationship was evident with the L_A allele, with the lifetime prevalence of PTSD increasing from two percent to four percent and six percent for subjects with zero, one and two L_A alleles, respectively. An interaction was also found between 5-HTTLPR polymorphisms and number of traumatic events. Of those who did not experience three or more traumas, the absolute risk for PTSD was 3.1 percent for those without the L_A allele and 3.9 percent for those with the L_A allele; whereas for those who experienced three or more traumas, the risk was 3.7 percent for those without the L_A allele and 12.8 percent for those with the L_A allele. These results indicate both an additive effect and a gene-interaction effect for the L_A allele of the serotonin transporter gene promoter on PTSD risk, but further study is needed to confirm these findings.

Grabe, H.J., Spitzer, C., Schwahn, C., Marcinek, A., Frahnow, A., Barnow, S., et al. (in press). Serotonin Transporter Gene (SLC6A4) Promoter Polymorphisms and the Susceptibility to Posttraumatic Stress Disorder in the General Population. *The American Journal of Psychiatry*.

ASSESSMENT AND TREATMENT

Topiramate in combat-related posttraumatic stress disorder

Sample: Male combat veterans with PTSD

N = 43 enrolled, 29 completed

Variables: Topiramate, PTSD, sleep, alcohol consumption

Key findings: When used as an add-on therapy, topiramate may be effective in reducing symptoms of combat-related PTSD, high-risk alcohol intake and nightmares.

Summary and implications: Pharmacotherapy for PTSD typically involves the use of anti-depressants, but there is some indication that the anti-convulsant drug topiramate could be helpful in reducing nightmares associated with PTSD. Some research also suggests topiramate could assist in the management of alcoholism, which is very prevalent among combat veterans with PTSD. An eight-week pilot study of

topiramate was conducted with 43 male combat veterans with PTSD. Psychometric, sleep and alcohol consumption assessments were conducted at baseline and at the eight-week follow-up. Analyses were conducted on the 29 subjects who completed the study. A significant reduction in general PTSD symptoms was found at follow-up as measured by the CAPS, and significantly fewer subjects reported having nightmares at the end of the study. Although not statistically significant, there was also a decrease in Stanford Sleepiness Scale scores and a decrease in subjects reporting high-risk alcohol consumption. These findings suggest that topiramate may be useful in reducing alcoholism, nightmares and other symptoms of combat-related PTSD, but larger, randomized trials must be conducted first to confirm these findings.

Alderman, C.P., McCarthy, L.C., Condon, J.T., Marwood, A.C. & Fuller, J.R. (2009). Topiramate in combat-related posttraumatic stress disorder. *The Annals of Pharmacotherapy*, 43 (4), 635-41.

Injury-specific predictors of posttraumatic stress disorder

Sample: American military personnel injured during combat between September 2004 and February 2005.

N = 831

Variables: Injury severity, injury type, blood pressure, PTSD, mental health diagnoses

Key findings: Diagnosis of any mental health condition and diagnosis of PTSD were predicted by the severity of the injury received.

Summary and Implications: Physical injury has been shown to be a risk factor in the development of PTSD, however, the relationship between injury severity and PTSD has not been definitively determined. Post-injury physiological measures, such as elevated heart rate and blood pressure, may also help predict the development of PTSD. The aim of this study was to investigate injury-related factors and physiological measures for their effect on development of PTSD in combat-injured military personnel. Previously gathered information on 831 male, combat-injured military personnel was obtained from the United States Navy – Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database. Physiological measures were recorded within a day of injury. Patients were followed for approximately two years after combat for diagnosis of PTSD or any other mental health condition. During the follow-up period, 31.3 percent of the patients were diagnosed with a mental health condition and 17 percent were diagnosed with PTSD. Increased injury severity was a significant predictor of diagnosis of any mental health condition or PTSD. Gunshot wound injuries also carried an increased risk of any mental health or PTSD diagnosis. Diastolic blood pressure was associated with any mental health diagnosis, and this relationship was modified by injury severity. The results of this study suggest a need for increased mental health screening of specific groups of combat-injured personnel.

Macgregor, A.J., Corson, K.S., Larson, G.E., Shaffer, R.A., Dougherty, A.L., Galarneau, M.R., et al. (2009). Injury-specific predictors of posttraumatic stress disorder. *Injury*, 40 (9), 1004-10.

Histone deacetylase inhibition combined with behavioral therapy enhances learning and memory following traumatic brain injury

Sample: Male brain-injured mice and control mice

N= 86

Variables: Histone deacetylase (HDAC) inhibitor, memory, learning, fear conditioning

Key findings: Learning and memory improved when sodium butyrate, an HDAC inhibitor, was administered at the same time as training in the Morris water maze task in brain-injured mice.

Summary and implications: Environmental enhancement is thought to improve plasticity and recovery in brain-injured animals through epigenetic changes that enhance histone acetylation. This study sought to recreate this effect by administering sodium butyrate, an HDAC inhibitor, to brain-injured mice. The results showed that when the sodium butyrate was administered during or after neurodegeneration but before behavioral training in the Morris water maze task, there was no improvement in memory or learning. However, when the sodium butyrate was administered during training in the Morris water maze task (after neurodegeneration), learning and memory improved in the brain-injured mice. These mice also showed a subsequent continued improvement in a foot-shock fear-conditioning task. These results lead the authors to conclude that administration of an HDAC inhibitor mimics some of the cognitive improvements caused by environmental enhancement in brain-injured animals, but only when the treatment is concurrent with behavioral training.

Dash, P.K., Orsi, S.A. & Moore, A.N. (in press). Histone deacetylase inhibition combined with behavioral therapy enhances learning and memory following traumatic brain injury. *Neuroscience*.

A comparison of PTSD symptom patterns in three types of civilian trauma

Sample: Trauma-exposed female college students

N = 433

Variables: PTSD symptomatology, trauma type

Key Findings: Trauma from sexual abuse is associated with more severe PTSD symptoms than trauma from motor vehicle accidents or the sudden and unexpected death of a loved one. Additionally, symptom patterns of PTSD can vary by trauma type. These findings indicate differing traumas may require different treatment approaches.

Summary and Implications: Studies have shown that distinct traumas are associated with different conditional risk for developing PTSD. However, it is unknown whether different types of trauma produce different patterns of PTSD symptomatology. Included in this study were 433 women who had directly experienced, witnessed or learned about a traumatic event; 162 had experienced a motor-vehicle accident (MVA), 86 had experienced a sexual assault (SA), and 185 participants had experienced a sudden and unexpected death of a loved one (SUD). Significant group differences in symptom clusters existed between the three types of traumatic events, with SA consistently scoring higher on most PTSD Checklist-Specific (PCL-S) items, including total Cluster B, C and D scores and

overall PCL-S score. Additionally, the study found that PTSD symptom pattern varied by trauma type. For instance, symptoms related to interpersonal loss, such as restricted range of affect, avoidance of feelings and detachment, were more severe in SA and SUD than in MVA. Given that different trauma types may result in variations in PTSD symptom patterns and severity, patients may benefit from treatments tailored according to trauma type. These findings may also have implications for PTSD diagnostic criteria.

Kelley, L.P., Weathers, F.W., McDevitt-Murphy, M.E., Eakin, D.E. & Flood, A.M. (2009). A comparison of PTSD symptom patterns in three types of civilian trauma. *Journal of Traumatic Stress*, 22 (3), 227-35.

Quetiapine ameliorates anxiety-like behavior and cognitive impairments in stressed rats: implications for the treatment of posttraumatic stress disorder

Sample: Adult male rats

N= 52

Variables: Quetiapine, anxiety, cognitive impairment, extracellular-regulated protein kinase (ERK) expression

Key findings: Rats that were exposed to enhanced single prolonged stress (ESPS), an animal model of PTSD, showed significantly less anxiety-like behavior and cognitive impairment when administered quetiapine daily.

Summary and implications: New evidence has shown that atypical antipsychotic medications can be used to augment therapy in PTSD patients who display poor response to antidepressants. The aim of this study was to examine if administration of quetiapine, an atypical antipsychotic, results in protective and preventative effects against anxiety-like behavior and cognitive impairment in rats exposed to an animal model of PTSD. Enhanced single prolonged stress (ESPS) involves forced swimming and electric foot shocks to induce stress in the rats to create conditions similar to PTSD. This study also sought to examine the effects of quetiapine on levels of pERK 1/2, a protein highly sensitive to stress, in specific regions of the rats' brains. The rats were orally administered quetiapine for 14 days before or after the ESPS procedures. The rats were given an open-field test to measure their spontaneous locomotor activity, an elevated plus-maze test to measure their responses to external stressful stimuli, and a Morris water maze test to measure their learning and spatial memory performance. The results showed that rats exposed to ESPS showed significantly less anxiety-like behavior and cognitive impairment when administered quetiapine daily (either pre- or post-ESPS exposure), compared to the rats exposed to ESPS that did not receive quetiapine. The rats that received quetiapine (either pre- or post-ESPS exposure) showed significantly elevated levels of pERK 1/2 in the prefrontal cortex, medial amygdala nucleus, and cingulate gyrus after ESPS compared to rats not given quetiapine, who showed decreased pERK1/2 in these three areas after ESPS. These findings suggest that quetiapine has preventative and protective effects against stress-related symptoms. Also, the pERK 1/2 level differences shown in this study suggest this protein may be associated with the pathophysiology of PTSD and should be further investigated

as a biomarker. This study also demonstrated that cognitive impairments may be an important symptom cluster in individuals with PTSD. Treatment with quetiapine should be further investigated in humans for its efficacy in preventing and protecting against PTSD symptoms.

Wang, H.N., Peng, Y., Tan, Q.R., Chen, Y.C., Zhang, R.G., Qiao, Y.T., et al. (in press). Quetiapine ameliorates anxiety-like behavior and cognitive impairments in stressed rats: implications for the treatment of posttraumatic stress disorder. *Physiological Research*.

Pilot controlled trial of d-serine for the treatment of post-traumatic stress disorder

Sample: Adult chronic PTSD patients

N = 22 enrolled, 16 completed

Variables: d-serine, PTSD, anxiety, depression

Key findings: Enhancement of NMDAR glutamate receptor function via d-serine may be effective in reducing symptoms of PTSD and anxiety in chronic PTSD patients.

Summary and implications: Pharmacological interventions targeting neurotransmission at the N-methyl-D-aspartate subtype of glutamate receptors (NMDAR) may be an effective new strategy in the treatment of PTSD. To test this hypothesis, the authors investigated the use of d-serine (DSR), a full agonist (activator of neurotransmission) at the NMDAR-associated glycine site, as a potential treatment for chronic PTSD. In this double-blind crossover trial, 22 chronic PTSD patients were randomized to receive either DSR or placebo for six weeks, then after a three-week washout, were given the opposite treatment for six weeks. Treatment with DSR resulted in a statistically significant reduction in PTSD and anxiety symptoms when compared to placebo. These findings indicate that pharmacotherapy targeting NMDAR glutamate receptors may be effective in treating PTSD, and further trials are warranted.

Heresco-Levy, U., Vass, A., Bloch, B., Wolosker, H., Dumin, E., Balan, L., et al. (in press). Pilot controlled trial of d-serine for the treatment of post-traumatic stress disorder. *The International Journal of Neuropsychopharmacology*.

HEALTH AND FUNCTIONING

Subsyndromal posttraumatic stress disorder is associated with health and psychosocial difficulties in veterans of Operations Enduring Freedom and Iraqi Freedom

Sample: OEF/OIF veterans

N = 557

Variables: PTSD, health, social functioning

Key Findings: Partial PTSD is associated with impaired health and psychosocial functioning; PTSD diagnostic criteria may be too restrictive to identify all those who need help.

Summary and Implications: PTSD has been associated with diminished health and psychosocial functioning in veteran populations. However, many veterans have clinically significant

trauma-related symptoms that do not meet full diagnostic criteria for PTSD (termed in research as partial PTSD), and the consequences of these symptoms have not been well studied. Five hundred and fifty-seven Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans completed surveys on their general health, psychosocial functioning and PTSD symptoms. Approximately one-fifth of the sample (21.5 percent) met criteria for a full PTSD diagnosis, while 22.3 percent met the partial PTSD criteria. Veterans with partial PTSD reported levels of health and psychosocial functioning (such as dealing with family, work and relationship issues) that were significantly poorer than veterans with no PTSD, but better than veterans with full PTSD. The results of this study suggest that partial PTSD is associated with impairments in health and psychosocial functioning, and veterans with partial PTSD may be overlooked by the current PTSD diagnostic criteria for the purpose of receiving needed resources and treatments.

Pietrzak, R.H., Goldstein, M.B., Malley, J.C., Johnson, D.C. & Southwick, S.M. (in press). Subsyndromal posttraumatic stress disorder is associated with health and psychosocial difficulties in veterans of Operations Enduring Freedom and Iraqi Freedom. *Depression and Anxiety*.

Psychosocial buffers of traumatic stress, depressive symptoms, and psychosocial difficulties in veterans of Operations Enduring Freedom and Iraqi Freedom: The role of resilience, unit support, and postdeployment social support

Sample: OEF/OIF veterans

N = 272

Variables: Social support, resilience, PTSD, depression

Key findings: Resilience, unit support, and postdeployment social support act as buffers against the development of PTSD, depressive symptoms and postdeployment psychosocial problems.

Summary and implications: Most research to date has examined risk factors for developing PTSD, while little has been focused on protective factors against developing the condition. This study measured resilience, an individual service member's ability to adapt and change in stressful situations, as a protective factor against PTSD and depressive symptoms. Two hundred and seventy-two Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans completed surveys on social support, psychological resilience, psychosocial functioning, and PTSD and depression symptoms. Unit support and postdeployment social support are negatively correlated with PTSD and depressive symptoms and positively correlated with resilience and psychosocial functioning (postdeployment support only). Resilience fully mediated the relationship between unit support and PTSD and depressive symptoms. In addition, postdeployment social support partially mediated the relationship between PTSD and depressive symptoms and psychosocial difficulties. Social support may enhance psychosocial functioning by promoting effective coping strategies, reducing high-risk behaviors, fostering self-efficacy and reducing loneliness. The findings from this study suggest that interventions designed to

bolster unit support, resilience, and postdeployment social support may help protect against PTSD and depressive symptoms.

Pietrzak, R.H., Johnson, D.C., Goldstein, M.B., Malley, J.C., Rivers, A.J., Morgan, C.A., et al. (in press). Psychosocial buffers of traumatic stress, depressive symptoms, and psychosocial difficulties in veterans of Operations Enduring Freedom and Iraqi Freedom: The role of resilience, unit support, and postdeployment social support. *Journal of Affective Disorders*.



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